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Primary attenuation of the aging process in humans: an integrative approach

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ABSTRACT

Human life span depends upon a multitude of factors. Aging results in a reduced ability to respond to stress, imbalance in homeostasis and an increased susceptibility to disease. This cellular sensecne is related to the shortening of telomeres with each cell cycle. At a certain reduction in the telomere length, the cells die. The aim of primary attenuation of the aging process lies in slowing this "molecular clock". Although not yet successful in humans, life has been extended in mice 2.5 times, yeast 15 times and nematodes 10 times under controlled laboratory conditions. This article looks at some promising integrative approaches towards life span extension in humans.

Keywords: Anti-aging, lifespan, caloric restriction, DHEA, Melatonin.

Abbreviations: LDL-low density lipoprotein, HDL-high density lipoprotein, IMT-intima-media thickening, CR-calorie restriction, DHEA- dehydroepiandrosterone, DHEAS- sulphate ester of dehydroepiandrosterone, DNA- Deoxyribonucleic acid

1. INTRODUCTION

Humans have been searching for therapeutic interventions that can prolong life throughout the ages. Most civilizations have attempted to create an "elixir of immortality" but life expectancy has been dismally low till recently. During the time of Plato or Julius Cesar, life expectancy was 28 years. Even in early 20th century, life expectancy was only about 47 years in the United States. In the recent 1950's, people in China and India were expected to live only about 35 years. However, there has been a tremendous increase in life spans over the last 50-100 years. As a matter of fact, a child born in the USA today can expect to live to 100 years. The major improvement has been from multiple factors - lower infant mortality rate and advances in medical health such as antibiotics and vaccination, along with better nutrition. However, this increase has been primarily due to a 'secondary' age prolongation.

Currently, major secondary contributors to reduced longevity are cancer and cardiovascular disease. And lifestyle factors such as smoking, dietary intake, energy balance, and adiposity are responsible for up to 70% of these chronic diseases (Herskind et al, 1996, Eyre et al, 2004). Although awareness of this is widespread, smoking especially in the developing countries, and obesity and diabetes all over the world continues to rise.

2. INTEGRATIVE INTERVENTIONS

Simple lifestyle changes or supplementation with over the counter agents may help slow the biological clock of aging.

2.1. Caloric Restriction

Caloric restriction in intervention studies in humans has been shown to positively impact chronic diseases. In the study, test subjects ate 10-25% less calories than the controls over several years. The calorie-restricted group fared much better than the control group in terms of average total and LDL cholesterol, higher HDL and lower triglycerides levels. They also exhibited lower blood pressure, fasting glucose, fasting insulin (67% reduction), body mass index, body fat percentage, C-reactive protein, carotid IMT (40% reduction), and platelet-derived growth factor AB (Proc Natl Acad Sci., 2004). These changes result in a lower future incidence of heart attack, stroke, diabetes and cancer. Epidemiological data has confirmed this. There was a sharp decrease in coronary heart disease mortality during World War II due to food shortages in some European countries, and this reversed after the war ended (Strom et al, 1951, Hindhede, 1921). Japanese living on the Okinawa island, generally eat 30% less calories than the average Japanese population, and exhibit approximately 35% lower rates of cardiovascular disease and cancer mortality (Kagawa, 1978). Similar changes were reported during the food shortages in Cuba during the period of 1989 and 2000. Deaths caused by diabetes declined by 51%, coronary heart disease mortality dropped 35% and stroke mortality by 20% (Franco et al, 2007). These reductions in chronic diseases should translate into an increased life expectancy. However, caloric restriction - an intake of about 25% of the daily intake but in a nutritionally balanced mode also brings about hormonal and cellular changes that may bring about 'primary' age prolongation. Such a caloric restriction has been documented to increase the lifespan in a variety of species, including yeast, fish, rodents and dogs. In mice and rats, life span increases of 30-40% are seen. (Mattson, 2005) In primates, studies with calorie restriction are showing positive results, suggesting a possible increase in life span (Mattson et al, 2009, Rezzi et al, 2009).

The main mode of action of caloric restriction appears to be reduced insulin levels and associated increased autophagy (Cuervo et al, 2005). The process of autophagy allows sequestration and degradation of organelles and macromolecular constituents of cytoplasm, which allows cellular restructuring and repair. It also provides a source of nutrients during early starvation. Since autophagy declines with increasing age, ad libitum eating leads to reduction in cell functions due to toxic accumulation of altered structures. Increased autophagy is good - it helps keep the cells clean and live longer. Although exercise may have a similar action in terms of energy balance, and also improve cardiovascular and metabolic markers, when compared with caloric restriction, CR animals live much longer than exercised animals (Washington University School of Medicine, 2006). This is because exercise is unable to fully mimic the hormonal and/or metabolic response to calorie restriction. One major study found that besides a reduction in fasting insulin levels, caloric restriction also brought about a reduction in body temperature, indicating that the metabolic rate is reduced more than that expected from the reduced metabolic body mass (Leonie et al, 2006).

In humans, a 25% calorie restriction with an otherwise nutritionally sound diet results in weight loss and significant health benefits. It is still unclear whether the associated improvement of biomarkers of aging, translate into a longer life span or not. The ongoing CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) trials by the National Institute of Aging should shed more light on this phenomenon.

2.2. DHEA

Another interesting hormone is DHEA (dehydroepiandrosterone), with data indicating that high levels may prolong life, especially in men. DHEA and its sulfate ester DHEAS are produced by the adrenal glands and are converted into potent androgens and estrogens in the peripheral tissue (Labrie F, 2005). DHEAS exhibit immuno-enhancing, anti-diabetic, anti-obesity, anti-cancer, neurotrophic, memory-enhancing and anti-aging effects (Yen , 2001). However, the body levels of DHEAS, after reaching a peak between the ages of 20 and 30, decrease markedly, and by the age of 70, the levels fall to approximately 20% of their peak values (Khaw, 1996). A recent prospective study in a community-based cohort revealed that high DHEAS levels were a predictor of longevity in men but not in women (Enomoto et al, 2008).

2.3. Fish Oils and Vitamin D

Another life extending supplement may be fish oils. In a report published in the JAMA, high levels of omega-3 fatty acids in people with heart disease correlated with a lower rate of shortening of telomere length - a marker for aging. (Farzaneh-Far et al, 2010) A telomere protects the end of the chromosome from deterioration. This is the region of the replicative DNA on a chromosome and its length is a marker of biological aging. Shortening blocks cell division and enhances aging. Besides omega-3 fatty acids, higher vitamin D levels are also associated with longer leukocyte telomere length, and Vitamin D supplementation may play an important

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role in increasing longevity (Richards et al, 2007). Telomere length is also adversely affected by elevated levels of oxidative stress and inflammation (De Meyer et al, 2008). Like calorie restriction, supplementation with these agents may provide both primary and secondary protection against premature aging.

2.4. Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine) is an endocrine hormone produced by the pineal gland, and helps regulate the sleep-wake cycle by chemically causing drowsiness and lowering the body temperature. Melatonin administration or blindness (increased melatonin levels due to constant darkness) increases the life span of rats (Lehrer, 1981). Melatonin is a potent free radical scavenger and its deficiency may result in reduced antioxidant activity in the elderly and this may have anti-aging significance. It also exhibits immunomodulatory properties and may help favorably remodel the immune system function and help extend aging (Karasek, 2004, Karasek , 2002).

2.5. Other Supplements

It has been suggested that antioxidant supplements may extend human life by preventing free radical damage. Several hormones like oxytocin, insulin, erythropointin and human chorionic gonadotropin may also play a role in life extension. Substances like resveratrol, and minerals like selenium or zinc may have life extending properties in nematodes and rats. The ability of these agents to extend life in humans is however unproven to date.

3. CONCLUSION

Although preliminary, these studies on attenuating the aging process in humans are very promising. All conventional and integrative physicians, while incorporating these findings in their own lives, should also consider imparting this information to their patients, with the hope of making them not only living healthier, but longer.

SUMMARY

1. The major cause of increased life span in the humans over the last few centuries has been due to a lower infant mortality and advances in medical health such as antibiotics and vaccination.
2. Primary attenuation of life span has eluded humans
3. Understanding the mechanisms behind telomere shortening and targeting lifestyle changes and agents to reduce this may help increase life span through primary attenuation.

FUTURE ISSUES

Is primary attenuation of the aging process possible? If yes, could this lead to an eventual immortality?

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Conflicts of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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